-- 61. A soluble fragment of a homogeneous protein which (i) has an apparent molecular weight of about 55 kilodaltons on a nonreducing SDS-polyacrylamide gel, (ii) binds human tumor necrosis factor, and (iii) is recombinantly produced in a host cell from a DNA sequence that is heterologous to the host cell, the fragment comprising the amino acid sequence Leu-Val-Pro-His-Leu-Gly-Asp-Arg-Glu-Lys-Arg-Asp-Ser-Val-Cys-Pro-Gln-Gly-Lys-Tyr-Ile-His-Pro-Gln-X-Asn-Ser-Ilein which X stands for a non-determined amino acid residue. --

REMARKS

Reconsideration is requested in view of the following remarks. Claims 44-47 and 55-56 were pending in the subject application and claim 55 has been withdrawn from consideration by the Patent Office. Applicants have hereinabove canceled claims 47 and 59, without prejudice to filing these claims in a further application that claims the benefit of the subject application's filing date under 35 U.S.C. §120, amended claim 44, and added new claims 60-61. Accordingly, claims 44-46, 56-58, and 60-61 are under consideration at this time.

New claims and support for amendment

New claims 60-61 are fully supported by the specification and correspond to claims 47 and 59 written in independent form (clerical modifications have been made to aid in readability). Claim 44 has been amended to delete the word "insoluble" and insert the word "receptor". This amendment is supported throughout the specification and specifically at page 7, lines 13-18.

Allowable claims

The Patent Office has indicated that claims 47 and 59 would be allowable if rewritten in independent form to include all limitations of the base claim and any intervening claims. Corresponding claims 60 and 61 are therefore maintained to be allowable.

35 U.S.C. §112 rejection

Claims 44, 45, and 56 were rejected under 35 U.S.C. §112, first and second paragraphs, because the term "insoluble" provides either a lack of enablement or an inconsistency in nomenclature.

Applicants have amended claim 44, the base claim from which claims 45 and 56 depend, to eliminate the word "soluble" and recite the word "receptor". Applicants agree

that their inventive material is a homogeneous protein that has been obtained from solubilized membranes and that such fact would have been obvious to a skilled artisan who had read the specification. The word "insoluble" was used to indicate that the native form of the protein is insoluble, i.e. the protein when in the membrane. The word "receptor", which is fully supported by the specification, conveys that applicants' claimed protein and fragments can be obtained from cell membranes, as opposed to soluble human tumor necrosis factor binding protein, such as that found in urine.

In view of the above clarification, it is clear that applicants' protein of claims 44, 45, and 56 corresponds to an insoluble protein that has been solubilized and homogenized. In view of this clarification, the application of the word "insoluble" to applicants' claimed protein presents no issues under 35 U.S.C. § 112. Applicants request reconsideration, and withdrawal of this rejection.

Claims 44, 46, 47, and 58 were rejected under 35 U.S.C. §112, first paragraph, because the specification does not reasonably provide enablement for all of the polypeptides which are 55 kDa which bind to human tumor necrosis factor ("TNF"). Specifically, the Office Action alleged that antibody fragments having an apparent molecular weight of 55 kDa could fall within the scope of applicants' claims yet not be

enabled. The Patent Office acknowledged, however, that the TNF receptor polypeptides identified by sequences set forth in Figures 1 and 4 are enabled.

The word "receptor" that now appears in the claims requires that applicants' claimed protein and soluble fragments thereof be of receptor origin, as distinguished from soluble origin, such as from urine. The word "receptor" also precludes other proteins from falling within the claims, such as the antibody fragments suggested in the Office Action.

In view of the above, applicants request reconsideration of the rejection under 35 U.S.C. § 112, first paragraph. Applicants maintain that all claims fully comply with 35 U.S.C. § 112, and request that all such rejections be withdrawn.

35 U.S.C. §102 rejection

Claims 44, 46 and 58 were rejected under 35 U.S.C. §102(e) as allegedly unpatentable over Smith (U.S. Patent No. 5,395,760).

The invention of claim 44 relates to a homogenous 55 kD receptor protein which binds TNF. The invention of claim 46 relates to a homogenous 55 kD protein, or a soluble fragment thereof, which binds TNF and is recombinantly produced in a host cell from a DNA sequence heterologous to said host cell, which DNA sequence encodes

said protein or said fragment. The invention of claim 58 relates to a soluble fragment of a homogeneous protein which has an apparent molecular weight of about 55 kilodaltons on a nonreducing SDS-polyacrylamide gel and which binds human tumor necrosis factor, the fragment being capable of binding TNF and being recombinantly produced in a host cell from a DNA sequence that is heterologous to the host cell and that encodes the soluble fragment.

Applicants traverse the Patent Office's rejection based on Smith. A reference on which a §102 rejection is based must describe every element of the invention claimed [see In re Marshall, 198 USPQ 344 (CCPA 1978); Ex parte Levy, 17 USPQ2d 1462 (BPAI 1990)]. Smith does not describe every element of applicants' claimed protein and therefore cannot form a basis for a §102 rejection. Smith fails to describe a homogenous 55 kD protein or fragments thereof that bind human TNF.

Applicants maintain that In re Marshall and Ex parte Levy apply to their situation. In contrast to the position set forth in the Office Action, these cases stand for the proposition that a single reference must disclose every element of the claimed invention. Nowhere to these cases limit this proposition to structural limitations as suggested by the Patent Office. In fact, the claims in Marshall are directed to method

claims presented in Jepson format. Accordingly, it is incumbent on the Patent Office to address every element of applicants' claims.

As mentioned previously, Smith relates to the "mature full-length human TNF-R" which is "a glycoprotein having a molecular weight of about 80 kilodaltons" (see Smith at column 3, lines 47-49, and column 7, lines 14-20). The only mention of a 55 kD TNF-R in Smith is found in the "Background of the Invention" section describing the prior art. For convenience, the entire portion mentioning 55 kD TNF-R is reprinted below:

> More recently, two separate groups reported the molecular cloning and expression of a human 55 kDa TNF-R (Loetscher et al., *Cell*, 61:351, 1990; Schall et al., *Cell*, 61:361, 1990). The TNF-R of both groups has an N-terminal amino acid sequence of the urinary binding protein disclosed in UK 2 218 101 A. Engelmann et al. (1989) and Engelmann et al. (1990).

Applicants again point out that all of the documents cited in the above passage from Smith et al. have been considered by the Patent Office and no rejection was made in the present application.[1]

Furthermore in addition to Smith providing no meaningful disclosure with respect to the 55 kD TNF-R, the Patent Office is not entitled to its reliance on Smith. The portion of Smith identified above was added at the time of filing Serial No. 523,635. This portion of the Smith disclosure is only entitled to a May 10, 1990 filing date, not the

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[1] These documents were discussed at length during the prosecution of the parent patent application (now US Patent No. 5,610,279).

date of the earlier Smith priority documents. All three of applicants' Swiss priority document predate the disclosure of Smith. **Therefore, the portion of Smith relied upon by the Patent Office has an effective date after applicants' priority date and is not prior art.**

In view of the above, applicants request that the Patent Office reconsider and withdraw all rejections under 35 U.S.C. § 102.

Information Disclosure Statement

In connection with their Amendment dated February 25, 1997, applicants filed a Supplemental Information Disclosure Statement. Applicants have not received a copy of the initialed form PTO-1449 indicating that the cited document have been considered. Accordingly, applicants reiterate their request for a copy of the initialed form PTO-1449 to applicants.

Merely for completeness, applicants point out that a new Smith et al. patent has issued, U.S. Patent No. 5,712,155, dated January 27, 1998. Since this patent is a continuation of Smith, it is maintained to be merely cumulative. A courtesy copy is enclosed for your file.

Based upon the above, applicants request reconsideration, withdrawal of all rejections, and issuance of a Notice of Allowance.

If a telephone conference would be of assistance in furthering prosecution of this application, applicants' undersigned attorney request that he be contacted at the number provided.

No fee, except the fee for a three-month extension of time, is required in connection with the filing of this Amendment. If any fee is deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,

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